Acquisition Challenges of a **Lethal Virus**

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It's 1995. "The Hot Zone" tops best-seller lists, and millions of people the world over are fixated on the threat of incurable "hot" hemorrhagic fever viruses like Ebola. Gruesome depictions of melting skin and oozing blood fill television and movie screens everywhere—but it's not science fiction.

Amid the panic and uncertainty, I am deployed to Zaire, where an outbreak of Ebola is occurring. As an entomologist with the Army Medical Research Institute of Infectious Diseases, I have expertise that will help determine whether the virus is insect-borne.

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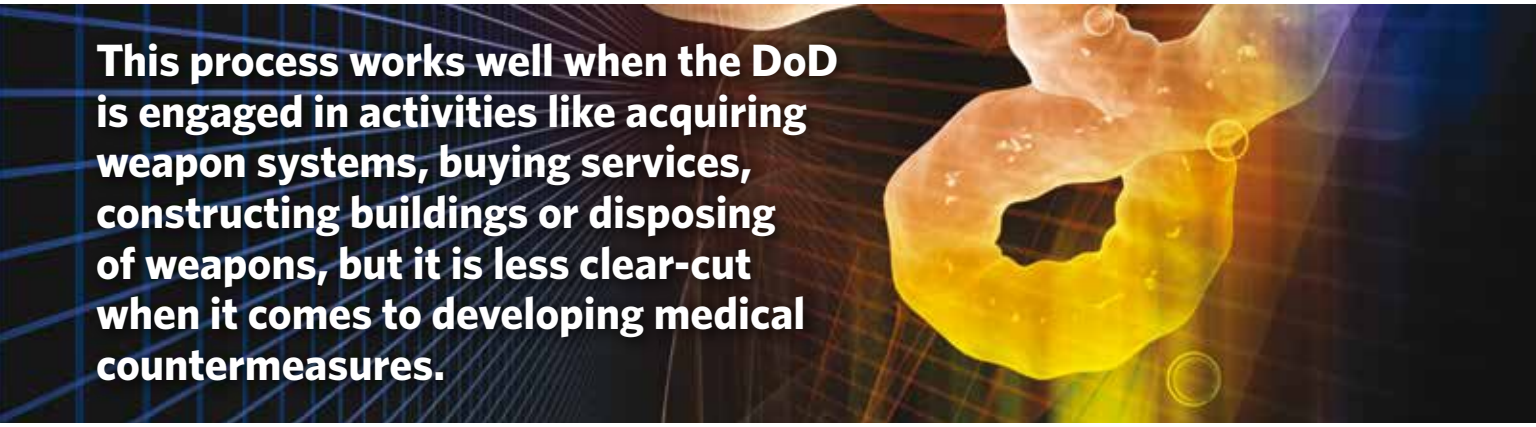
I board the plane and leave behind my wife, who is seven months pregnant. On the tarmac in Kinshasa, I think about the unknowns: How is the virus transmitted? How will I protect myself? Will I bring the virus back home? The only thing I know for sure is this: There is no treatment for the virus I am going to track down.

Advancing Medical Countermeasures

Fast forward nearly two decades, and I am leading an organization charged with developing drugs, vaccines and medical devices to treat emerging infectious diseases—like the Zaire Ebola virus that I was sent to investigate in 1995. The organization, within the Department of Defense (DoD) Chemical and Biological Defense Program, is called the Joint Project Management Office of Medical Countermeasure Systems (MCS). It plays a vital role in implementing the DoD's strategy to prevent, diagnose and treat the effects of chemical, biological, radiological and nuclear (CBRN) threats and emerging infectious diseases.



This process works well when the DoD is engaged in activities like acquiring weapon systems, buying services, constructing buildings or disposing of weapons, but it is less clear-cut when it comes to developing medical countermeasures.

Infectious diseases—whether naturally occurring or engineered with intent to harm—can cause serious consequences for a fighting force. Absenteeism due to illness, costly prolonged recovery, the loss of combat readiness and—in the case of Ebola virus—even death are challenges facing military commands.

MCS is determined to find medical countermeasures (MCM) for several viruses, including Ebola. Recognizing the high failure rate associated with drug and vaccine development, our strategy is to advance several promising candidates concurrently so that if one MCM fails, we can keep moving forward with the more successful options. This is the government's most cost-effective and efficient approach, because by the time some drugs fail, others with better track records have reached important milestones.

The Case for Targeting Ebola

MCS' interest in Ebola and other hemorrhagic fever virus (HFV) infections stems from their high mortality rates. Because HFVs can spread through aerosolization or direct contact with the body fluids of infected persons, DoD has validated and prioritized combating the threat of HFVs, whether naturally occurring or engineered. Along with the agents that cause smallpox, anthrax, plague, botulism and tularemia, HFVs are among six identified by the Centers for Disease Control and Prevention as the most likely to be used as biological weapons.

While some HFVs can cause relatively mild illnesses, many others cause severe, life-threatening diseases. Ebola is a type of HFV characterized by high fever and bleeding disorders. The Zaire species of Ebola virus in particular has been associated with periodic outbreaks in human populations with mortality rates reaching 90 percent.

Ebola virus continues to cause epidemics of lethal disease. A rapidly evolving outbreak in the West African country of Guinea was reported by the World Health Organization (WHO) on March 23, 2014. Since then it has spread to Sierra Leone and Liberia. As of July 3, 2014, WHO reported 779 clinical cases of Ebola virus disease, including 481 deaths—a 62 percent case fatality rate.

Acquisition Challenges to Protect the Fighting Force

An MCM to protect U.S. military forces from infectious disease agents like Ebola presents unique challenges in the DoD environment. The DoD acquisition process is complex and thorough for good reason. It is designed to manage risk, allocate resources and ensure that the government is acquiring useful technology. This process works well when the DoD is engaged in such activities as acquiring weapon systems, buying services, constructing buildings or disposing of weapons, but it is less clear-cut when it comes to developing MCMs.

Product variables and uncertainties. Despite technological and engineering challenges, the essential variables are known or somewhat predictable in the fields of weapons, services and construction. For example, we may identify that we need a platform to perform some specific activity, and we can determine that the technology is available. The DoD knows how to develop, integrate and test the equipment; when to replace it; and how to deliver it to the battlefield. While challenges

may arise in this process, there is an inherent amount of certainty in overcoming them.

MCMs are a different story. Viruses, for example, mutate. This immediately removes certainty when trying to develop or acquire an MCM against a specific virus. Beyond a virus' ability to rapidly mutate into other forms, the disease it causes may affect people differently. Symptoms of the same disease may appear and vary significantly from one person to the next. Therapeutics or vaccines to combat these viruses add to this uncertainty because individual reactions to them may differ as well. These variables are often very complex, requiring time to thoroughly understand.

High risk with low return on investment. The nature and backdrop of drug development must be understood and constant attention given to the realities of the industry. The oft-cited statistic is that new drug development takes 10 to 12 years and costs $1 billion. For example, large research and development pipelines may produce many potential candidate technologies in the early stages, but very few clear all of the subsequent required efficacy, safety and related hurdles of development. This results in a funnel, with many candidates entering the process and extremely few remaining viable to the end. Needless to say, it's a risky business.

Beyond the high risk of pursuing therapeutic development in general, the potential return on investment for an MCM is limited. Pharmaceutical companies spend billions of dollars on drug development for chronic diseases that can provide them sustainable profits. However, they typically do not significantly invest in developing vaccines or therapeutics for rare diseases with little recurring revenue potential. Let's face it: From a pharmaceutical company's point of view, the risk of being infected with Ebola is pretty small.

Obtaining DoD and FDA approval. These challenges are exacerbated by the fact that we must navigate not only the DoD acquisition landscape but also Food and Drug Administration (FDA) processes that determine the licensing of vaccines and approval of therapeutics. MCM development and production must work within, and conform to, FDA drug approval requirements in the U.S. Code of Federal Regulations Title 21. The FDA, which is outside the DoD, is required by law to approve all drugs, biologics and medical equipment before they are provided to the public, including to the military Services.

Essentially, the FDA process accomplishes the same goal for drug approval as the DoD acquisition process does for hardware—the FDA ensures that manufacturers provide only safe and effective drugs, biologics and medical equipment to the public. Each process has its own timelines and reporting and management procedures, as well as risk-reduction activities and decision points.

MCS synchronizes the DoD acquisition with the FDA approval process to move through the decision events required by both. Successful decisions allow the product to progress through the two processes to eventual fielding and use by Service members and the nation.

MCS' Strategy to Meet These Challenges

MCS' efforts are critical to our defense. We provide safe, effective and innovative medical solutions to counter CBRN threats by developing promising new technologies and guiding them through both DoD's acquisition process and the intricate FDA approval process. Our four Joint Product Management Offices and two Product Support Offices provide responses to these threats at distinct stages of the continuum of care through programs aimed at preventing, diagnosing and treating CBRN threats. An essential part of this continuum is treating those exposed to an infectious disease.

The TKM-Ebola Example

To provide a strong, layered defense against Ebola, MCS is developing vaccines to prevent the disease and therapeutics to treat it. Our vaccine candidate uses components for the Ebola—Sudan and Zaire—and Marburg viruses in a single formulation. Our anti-viral therapeutic, TKM-Ebola, has received a Fast Track designation from the FDA.

Finding products in the advanced stages of development. At MCS, we work with leaders in the pharmaceutical, biotechnology and medical device industries that have proven technology. Through a full and open competition, our product office for BioDefense Therapeutics (BDTX) found such a product in Tekmira's TKM-Ebola, a drug candidate based on a gene-silencing technique used by plants and animals called RNA interference (RNAi).

In the past decade, RNAi has become one of the most important innovations in the field of drug discovery and development. In fact, in 2006 the scientists who discovered the mechanisms of RNAi were awarded the Nobel Prize for Physiology or Medicine. Tekmira also employs the most widely adopted RNAi delivery technology to date—its proprietary lipid nanoparticle (LNP) technology. LNP is administered intravenously, and the delivery technology allows RNAi drugs to be encapsulated in tiny particles made of lipids (fats or oils) that can travel through the bloodstream to targeted disease sites. LNP formulations are manufactured by a proprietary method that is robust, scalable and highly reproducible. Additionally, LNP-based products have been reviewed by multiple FDA divisions for use in clinical trials. *[Editor's Note: For a general discussion of nanoparticles and their potential role in medical and military applications, see the following article in this issue.]*

In preclinical studies, the TKM-Ebola therapeutic demonstrated 100 percent protection from an otherwise lethal dose of Zaire Ebola virus when TKM-Ebola was used to treat previously infected non-human primates (Geisbert et al., *The Lancet*, Vol. 375, May 29, 2010). The product is under continued development to evaluate safety and efficacy.

The importance of FDA approval experience. MCS makes it a priority to work with industry leaders that have a proven track record in acquiring FDA approval. Tekmira's knowledge of the FDA process and its approved request for FDA's Fast Track designation are critical to bringing the TKM-Ebola therapeutic to the Service members as quickly as possible. The FDA grants Fast Track status to an MCM if it will treat or prevent a serious or life-threatening disease and demonstrates the potential to address unmet medical needs. This status gives Tekmira more frequent written and in-person access to the FDA and allows for Rolling Review, which is an opportunity for submitting the required regulatory documentation to the FDA as it is developed. This helps to compress review timelines because the FDA does not have to wait until all documentation and test results can be submitted at one time.

To conduct a clinical trial, MCS and Tekmira are utilizing ICON Development Solutions, a specialized contract research organization in Phase I-IV clinical studies with a proven track record of success. The TKM-Ebola Phase I clinical trial at the ICON facility in San Antonio, Texas, is assessing the safety, tolerability and pharmacokinetics of administering TKM-Ebola to healthy adult subjects. The trial is a randomized, single-blind, placebo-controlled study involving single ascending doses and multiple ascending doses of TKM-Ebola. As this drug moves through clinical testing, it could become the first FDA-approved therapeutic to treat disease caused by this deadly virus.

About JPM-MCS

JPM-MCS, a component of the Joint Program Executive Office for Chemical and Biological Defense, aims to provide U.S. military forces and the nation with safe, effective and innovative medical solutions to counter CBRN threats. JPM-MCS facilitates the advanced development and acquisition of medical countermeasures and systems to enhance our nation's biodefense response capability. For more information, visit www.jpeocbd.osd.mil.

The Ebola Threat—Revisited

Pursuing practical solutions to counter the complex threat of infectious diseases for the men and women who serve our country is the greatest professional challenge I have ever faced. I often reflect on how far we've come from those terrifying days in 1995. Back then, entire families and communities were being wiped out by the Ebola virus in Zaire. In the hospital in Kinshasa, I met a 70-year-old man who was his family's lone survivor. I think of the deep sadness in that man's eyes—and I return to work every day determined to continue our progress.

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Defense AT&L Wins 2014 APEX Award for Excellence

Defense AT&L magazine recently received an APEX Award for Excellence for magazines, journals and tabloids with issues of 32 pages or more. APEX 2014 awards were based on outstanding graphic design, editorial content and "overall communications effectiveness and excellence."

There were 2,075 entries in all categories from the United States, Canada and Australia, including many from major corporations and associations. APEX awards are an annual competition for publishers, editors, writers and designers who create print, Web, electronic and social media. The awards are sponsored by Communications Concepts Inc.

Assistant Art Director Tia Gray and Managing Editor Ben Tyree receive a 2014 APEX Award for Excellence for the *Defense AT&L* magazine.